A 5-Year Study of Patients with Pulmonary Tuberculosis Treated at Home in a Controlled Comparison of Isoniazid plus PAS with 3 Regimens of Isoniazid Alone *

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This report from the Tuberculosis Chemotherapy Centre, Madras, describes theprogress, over a 5-year period, of 341 patients with newly diagnosed, sputum-positive tuberculosis. All the patients were treated on a domiciliary basis. In the first year, the patients received, on the basis of random allocation, a standard regimen of isoniazid plus PAS or 1 of 3 regimens of isoniazid alone. Previous reports have shown that the response in the first year was substantially superior with the standard regimen, and that the bacteriological relapse rates in the second year were fairly similar for the 4 regimens. The findings in the present report extend the latter conclusion to the end of 5 years. Further, when considered together with the findings in an earlier study, they have shown that isoniazid, given as maintenance chemotherapy in the second year, was highly effective in preventing bacteriological relapse in patients who, at 1 year, had bacteriologically quiescent disease and no residual cavitation ; the effect was, however, less marked in patients with residual cavitation at 1 year.

Patients who were clear-cut failures of the allocated chemotherapy and those who had a bacteriological relapse in the second or subsequent years were usually re-treated with streptomycin plus PAS or streptomycin plus pyrazinamide, and if this was ineffective, with cycloserine plus thioacetazone or cycloserine plus ethionamide.

Considering the findings over the 5-year period for all patients, 16 died from non-tuberculous causes and 1 took his discharge prematurely. Of the remainder, 86% had bacteriologically quiescent disease at 5 years, 6 % had bacteriologically active disease and 8 % had died of tuberculosis. These findings confirm the value of well-organized domiciliary chemotherapy, which was established by an earlier report from the Centre, and are particularly encouraging for developing countries such as India, where tuberculosis is a major problem and resources are limited.

An earlier publication from the Tuberculosis Chemotherapy Centre, Madras (1960), reported a controlled comparison, for a year, of 3 regimens of isoniazid alone with a standard regimen of isoniazid plus p-aminosalicylic acid (PAS) in the domiciliary treatment of patients with pulmonary tuberculosis. It was found that isoniazid plus PAS was the best regimen and that isoniazid alone in a daily dosage of 400 mg was more effective in 1 dose than in 2, divided, doses. The progress in the second year of certain categories of these patients has already been reported by Velu et al. (1961a) and Ramakrishnan et al. (1962). The present report describes the progress in the second to fifth years of *all* the patients originally admitted to the comparison, and their disease status at 5 years.

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I. PLAN AND CONDUCT OF THE STUDY

CHEMOTHERAPY DURING THE 5-YEAR PERIOD

In the first year, patients were allocated at random to 1 of 4 daily oral regimens. The drug dosage was related to the patient's weight (for details, see Tuberculosis Chemotherapy Centre, Madras, 1960). For instance, for a patient weighing 100 lb (45.4 kg), the details were as follows:

Regimen	*Drug and daily dosage*
PH	Isoniazid 200 mg plus sodium PAS 10 g, given together in cachets in 2, divided, doses
HI-1	Isoniazid alone, 400 mg, in a single dose
HI-2	Isoniazid alone, 400 mg, in 2, divided, doses
H	Isoniazid alone, 200 mg, in 2, divided, doses

The mean daily dosage of isoniazid at the start of chemotherapy was 4.6 mg/kg of body-weight for the PH series, 8.7 mg/kg for the HI-1 and the HI-2 series and 4.5 mg/kg for the H series. The mean daily dosage of PAS (for the PH series) was 0.23 g/kg.

The treatment policy in the second year for patients with bacteriologically quiescent disease at 1 year (defined on page 3) has been fully described by Velu et al. (1961a). In brief, the patients were allocated at random to treatment in the second year with isoniazid alone (approximately 4.5 mg/kg of body-weight daily, in a single tablet) or to a placebo-calcium gluconate (500 mg daily, in a single tablet). During the third year, half (selected at random) of the patients treated with isoniazid in the second year continued to receive the drug; all the remaining patients received the placebo. All patients received the placebo in the fourth year and no medicament in the fifth year. However, chemotherapy was prescribed in a few instances on account of a bacteriological relapse; the numbers involved and the details are presented on pages 4-9. The policy was to treat all patients on a domiciliary basis.

The treatment prescribed to patients with disease of bacteriologically doubtful status at 1 year and to those with bacteriologically active disease at 1 year is described on page 9.

INVESTIGATIONS IN THE SECOND, THIRD, FOURTH AND FIFTH YEARS

Patients with bacteriologically quiescent disease at 1 year were assessed clinically and radiographically at monthly intervals in the second year and at 3-monthly intervals in the third, fourth and fifth years. The planned intensity of bacteriological examinations is set out in Table 1. The standard procedure was to obtain 14 specimens in the second year, 9 in the third, 9 in the fourth and 11 in the fifth year. Extra specimens were collected if a positive culture was obtained. An isoniazid sensitivity test was set up at each of these examinations if a positive culture was obtained. The techniques employed for smear and culture examination and sen-

TABLE 1

PLANNED INTENSITY OF BACTERIOLOGICAL EXAMINATIONS FOR PATIENTS WITH BACTERIOLOGICALLY QUIESCENT DISEASE AT 1 YEAR

Year	Month	Type and no. of specimens [a]	Total no. of specimens
2	13-23	1 collection specimen or a pair of laryngeal swabs	14
	24	2 collection specimens and a pair of laryngeal swabs	
3	27, 30 and 33	1 collection specimen and a pair of laryngeal swabs	9
	36	2 collection specimens and a pair of laryngeal swabs	
4	39, 42 and 45	1 collection specimen and a pair of laryngeal swabs	9
	48	2 collection specimens and a pair of laryngeal swabs	
5	51, 54 and 57	1 collection specimen and a pair of laryngeal swabs	11
	59 ½	1 collection specimen and a supervised spot specimen	
	60	2 collection specimens and a pair of laryngeal swabs	
Total specimens during the 4-year period of follow-up			43

[a] For the methods of obtaining the specimens, see Velu et al. (1961c).

sitivity tests, the details of the grading of smear and culture results, and the definition of isoniazid resistance have all been described elsewhere (Tuberculosis Chemotherapy Centre, Madras, 1960).

Patients with bacteriologically active or relapsed disease were assessed monthly throughout the period they were receiving chemotherapy. The monthly examinations included a chest radiograph, examination by smear and culture of 2 collection specimens of sputum, examination by culture of a pair of laryngeal swabs, and tests of sensitivity to the drugs the patients were receiving using techniques described previously (Tuberculosis Chemotherapy Centre, Madras, 1960; Angel et al., 1963; Ramakrishnan et al., 1967).

COLLAPSE THERAPY AND RESECTION

The policy was not to use collapse therapy or resection. In the event, 3 patients had surgical treatment (1 had a thoracoplasty, a second a plombage followed by a thoracoplasty, and the third a lobectomy).

CHANGE OF TREATMENT ON ACCOUNT OF RADIOGRAPHIC DETERIORATION

When the Centre's physicians considered that a definite radiographic deterioration had occurred, and that it persisted despite a course of penicillin, the full radiographic series was shown to an independent assessor (Dr K. S. Sanjivi), who decided whether a change of treatment was necessary.

DEFINITIONS USED IN THIS REPORT

At 1 year

Bacteriologically quiescent disease. All cultures (usually a total of 7-9) negative at 10, 11 and 12 months.

Disease of bacteriologically doubtful status. All cultures negative at 3 or more consecutive monthly examinations, but a single positive culture at 10, 11 or 12 months.

Bacteriologically active disease.

(a) A definite radiographic or serious clinical deterioration in the presence of a positive sputum, which necessitated a change of chemotherapy during the first year; or

(b) Cultures never all negative at 3 consecutive monthly examinations; or

(c) All cultures negative at 3 or more consecutive monthly examinations, but a *total* of 2 or more positive cultures at 10, 11 and 12 months.

During the second, third, fourth and fifth years

Isolated positive culture. A single positive culture, preceded by culture negativity for a 6-month period and succeeded by culture negativity for a 6-month period.

Bacteriological relapse. Two or more positive cultures in a 6-month period. This meant 2 or more positive cultures in 7 consecutive monthly examinations in the second year, or in 3 consecutive 3-monthly examinations in the subsequent years.

At 5 years

Bacteriologically quiescent disease. [1] All cultures (usually a total of 7-9) negative from 54 to 60 months, inclusive.

Bacteriologically active disease. A total of 2 or more positive cultures from 54 to 60 months, inclusive.

II. CLASSIFICATION OF PATIENTS AND PLAN OF THE REPORT

CLASSIFICATION OF PATIENTS

Of 341 patients who were admitted to the study, 96 were allocated to the PH, 75 to the HI-1, 75 to the HI-2 and 95 to the H regimen (Table 2). Altogether, 26 patients were excluded from the main analysis, 22 on account of isoniazid resistance on admission and 4 for miscellaneous reasons (Tuberculosis Chemotherapy Centre, Madras, 1960). The main analysis of the findings in the first year (Tuberculosis Chemotherapy Centre, Madras, 1960) concerned the remaining 315 patients (90 PH, 70 HI-1, 68 HI-2, 87 H) who (1) had cultures

[1] Included in this category are 12 patients (2 PH, 1 HI-l, 3 HI-2, 6 H), each of whom produced 1 positive culture between 54 and 60 months.

TABLE 2
CLASSIFICATION OF PATIENTS IN THE PRESENT REPORT

		Regimen				All regimens	Section in which progress is considered
		PH	HI-1	HI-2	H		
Patients included in the main analysis in the first year, according to the classificationof their disease status at *1 year*	(1) Bacteriologically quiescent disease	74	43	37	38	192	III
	(2) Disease of bacteriologically doubtful status	4	4	1	0	9	IV
	(3) Bacteriologically active disease	7	17	27	45	96	V
	(4) Change of treatment due to drug toxicity	2	5	1	0	8	VI
	(5) Death	3	1	2	4	10	–
	Total	90	70	68	87	315	
Patients excluded from the main analysis in the first year	(1) Isoniazid-resistant organisms on	6	3	7	6	22	VII
	(2) Miscellaneous reasons	0	2	0	2	4	
	Total	6	5	7	8	26	
All patients admitted to the study		96	75	75	95	341	VIII

sensitive to isoniazid on admission, (2) had had no previous chemotherapy (apart from 11 who had received up to 2 weeks of chemotherapy), and (3) had received the allocated chemotherapy for 12 months (apart from minor variations), unless they died or had a change of chemotherapy because of tuberculous deterioration or major toxicity. At 1 year, 192 of these patients had bacteriologically quiescent disease, 9 had disease of bacteriologically doubtful status and 96 had bacteriologically active disease; of the remainder, 8 had had their chemotherapy changed in the first year on account of drug toxicity and 10 had died (5 of tuberculosis and 5 of non-tuberculous causes).

PLAN OF THE REPORT

The plan of the report is set out in Table 2. The progress in the second, third, fourth and fifth years is described in Section III for patients with bacteriologically quiescent disease at 1 year, in Section IV for those with disease of bacteriologically doubtful status at 1 year, in Section V for those with bacteriologically active disease at 1 year, and in Section VI for patients whose treatment was changed during the first year on account of drug toxicity. Section VII reports the progress of the patients excluded from the main analysis, and Section VIII summarizes the disease status at 5 years of all the 341 patients admitted to the study.

III. PROGRESS DURING A 4-YEAR PERIOD OF FOLLOW-UP OF PATIENTS WITH BACTERIOLOGICALLY QUIESCENT DISEASE AT 1 YEAR

Of the 192 patients with bacteriologically quiescent disease at 1 year, 11 (4 PH, 2 HI-1, 1 HI-2, 4 H) were not allocated at random to treatment in the second year for reasons given by Velu et al. (1961a). Another patient (PH) had treatment restarted because she developed tuberculous lymphadenitis. The progress of these 12 patients is described on page 8.

Of the remaining 180 patients (69 PH, 41 HI-l, 36 HI-2, 34 H), 93 were allocated to isoniazid alone in the second year (isoniazid series) and 87 to calcium gluconate (placebo series). On the basis of a postero-anterior chest radiograph and tomograms, 54 of these were classified by an independent assessor (Dr Raj Narain) as having residual cavitation at

1 year (cavitated series) and 126 as having no residual cavitation (non-cavitated series). The progress of these 180 patients is now considered.

DEATHS

Altogether, 6 patients died during the 4-year period of follow-up. One patient (H, non-cavitated, placebo), who had a bacteriological relapse in the twentieth month, died from tuberculous meningitis in the forty-fifth month (see page 6). The remaining 5 patients died from non-tuberculous causes; 1 (HI-1, non-cavitated, isoniazid) died in the twenty-third month from diarrhoea with oedema, another (PH, cavitated, isoniazid) died in the twenty-eighth month following a cerebrovascular accident, another (PH, non-cavitated, placebo) committed suicide in the thirtieth month, a fourth (HI-l, cavitated, placebo) died in the forty-eighth month from *cor pulmonale,* and the fifth (H, non-cavitated, placebo), who was known to have bronchiectasis, died in the fifty-second month from repeated large haemoptyses associated with it. These 5 patients had had all cultures negative for at least 12 months immediately preceding death.

BACTERIOLOGICAL RELAPSE IN THE 4-YEAR PERIOD OF FOLLOW-UP

During the 4-year period of follow-up, 17 (9.4%) of the 180 patients had a bacteriological relapse, 10 (5.6%) in the second year (that is, the first year of follow-up), 2 (1.1 %) in the third, 3 (1.7%) in the fourth and 2 (1.1%) in the fifth year (Table 3). Thus, the risk of relapse was greatest in the second year.

Table 3 also presents the number of bacteriological relapses, year by year, according to:

(1) the chemotherapy in the first year (PH, HI-I, HI-2 or H);

(2) the cavitation status at the end of the first year (cavitated or non-cavitated); and

(3) the treatment in the second year (placebo or isoniazid).

The series in (1), in (2) and in (3) were compared for the condition on admission to initial treatment, and the condition at the end of the first year-that is, the starting point of the study of relapse. The findings have been reported earlier by Velu et al. (1961a); in brief, the series were similar, both initially and at 1 year, apart from the following exceptions: (1) the PH and the HI-1 series contained a higher proportion of patients who had larger lesions initially than did the HI-2 and the H series; (2) the PH, HI-1 and H patients had, on average, rather more extensive residual radiographic lesions at 1 year than the HI-2 patients; (3) the patients with cavitation at 1 year had, on average, more extensive radiographic lesions, both initially and at

TABLE 3

BACTERIOLOGICAL RELAPSE DURING THE 4-YEAR PERIOD OF FOLLOW-UP, RELATED TO CHEMOTHERAPY IN THE FIRST YEAR, CAVITATION STATUS AT 1 YEAR AND TREATMENT IN THE SECOND YEAR

		Total patients	Patients who had a bacteriological relapse					
			No.	%	Year of relapse			
					Second	Third	Fourth	Fifth
Chemotherapy in the first year	PH	69	9	*13*	5	1	1	2
	HI-1	41	3	*7*	2	0	1	0
	HI-2	36	2	*6*	2	0	0	0
	H	34	3	*9*	1	1	1	0
Cavitation status at 1 year	Cavitated	54	6	*11*	4	1	1	0
	Non-cavitated	126	11	*9*	6	1	2	2
Treatment in the second year	Placebo	87	15	*17*	9	2	3	1
	Isoniazid	93	2	*2*	1	0	0	1
All patients		180	17	*9.4*	10	2	3	2

1 year, than those without cavitation. Considering next the intensity with which patients were examined bacteriologically during the 4-year period of follow-up, analyses (not presented here) showed that it was broadly similar for the different series,

The proportions of patients who had a bacteriological relapse during the 4-year period were 13% of 69 PH, 7% of 41 HI-1, 6% of 36 HI-2 and 9% of 34 H patients (Table 3); none of the differences was significant ($P \geq 0.4$). Of 54 patients with cavitation at 1 year, 11% had a bacteriological relapse as compared with 9% of 126 patients with no cavitation. Finally, 17% of 87 patients in the placebo group had a bacteriological relapse as compared with 2% of 93 patients in the isoniazid group-a highly significant difference ($P = 0.001$).

Further analyses were undertaken to examine whether, as in a previous report (Velu et al., 1961a), the benefit from isoniazid in the second year was greater in the patients with no cavitation at 1 year than in those with cavitation. It was found that in the patients with residual cavitation, 5 (23%) of 22 in the placebo group had a bacteriological relapse as compared with 1 (3%) of 32 in the isoniazid group ($P=0.07$). In the patients with no cavitation at 1 year, 10 (15%) of 65 in the placebo group had a bacteriological relapse as compared with 1 (2%) of 61 in the isoniazid group, a highly significant difference ($P=0.01$).

In summary, the bacteriological relapse rate over the 4-year period did not appear to be influenced either by the chemotherapy in the first year or the cavitation status at 1 year. However, it was substantially lower in patients who received isoniazid in the second year than in those who received the placebo.

ISONIAZID ALONE IN THE THIRD YEAR

Of 93 patients who had received isoniazid alone during the second year, 1 died and 1 had a bacteriological relapse in the second year; the remaining 91 were allocated *at random* to treatment in the third year, 44 to placebo and 47 to isoniazid alone.

The intensity of bacteriological examination during the third, fourth and fifth years was similar for the 2 groups. During this period, there were no bacteriological relapses among the 44 patients in the placebo group as compared with 1 among the 47 in the isoniazid group; this patient (Table 4, A285) had a bacteriological relapse with isoniazid-resistant organisms in the fifty-fourth month.

DETAILS OF PATIENTS WHO HAD A BACTERIOLOGICAL RELAPSE

Table 4 gives the details for all the 17 patients who had a bacteriological relapse during the 4-year period. Clear-cut radiographic deterioration, confirmed by the independent assessor (Dr K. S. Sanjivi), occurred in 7.

Of the 17 patients, only 1 (A229) was receiving isoniazid at the time of the relapse; she had isoniazid-resistant organisms at the time of relapse. Of the remaining 16 (none of whom was receiving isoniazid at the time of the relapse), 12 yielded only isoniazid-sensitive cultures during the period of follow-up. Three patients (A229, A61, A20) had excreted isoniazid-resistant organisms during the *first year;* it is of interest that 2 of them had a relapse with isoniazid-sensitive organisms.

In all, 11 of the 17 patients were re-treated. Six of these, all of whom had a relapse with isoniazid-sensitive cultures, were re-treated with isoniazid plus PAS; 4 had bacteriologically quiescent disease at 5 years. Four patients were re-treated with streptomycin plus pyrazinamide, and all had quiescent disease at 5 years, and the remaining 2 had bacteriologically active disease. The eleventh patient was re-treated with streptomycin plus PAS and had only negative cultures from the second month onwards; however, 6 weeks after he had completed a year of re-treatment, he developed tuberculous meningitis and died 3 days after admission to a general hospital.

Considering the 6 patients who were not re-treated, the sputum became culture-negative spontaneously in 3 (A146, A61, A275) after 16, 2 and 5 months, respectively, and except for an isolated positive culture in 1 patient (A275), remained consistently negative up to 5 years. A fourth patient (All) had a relapse in the fourth year and then produced a series of negative cultures followed by positive cultures late in the fifth year. The remaining 2 (A31, A285) had a relapse in the fifth year, the second positive culture occurring at about 60 months.

In summary, of the 17 patients who had a bacteriological relapse, 11 had bacteriologically quiescent disease at 5 years, 5 had bacteriologically active disease and 1 had died from tuberculous meningitis.

VARIOUS FACTORS IN RELATION TO THE OCCURRENCE OF BACTERIOLOGICAL RELAPSE

The influence of various factors on the occurrence of bacteriological relapse in the 4-year period was

TABLE 4

DETAILS OF PATIENTS WHO HAD A BACTERIOLOGICAL RELAPSE, THEIR SUBSEQUENT CHEMOTHERAPY AND DISEASE STATUS AT 5 YEARS

Serial no.	Chemotherapy in first year	Cavitation status at 1 year	Treatment in the second year	Months at which 1 or more positive cultures were produced [a]	Total no. of positive cultures [a]	Results of isoniazid sensitivity tests [b]	Clear-cut radiographic deterioration	Month re-treatment started	Re-treatment chemotherapy [c] (months)	Disease status at 5 years
A146	PH	Cavitated	Placebo	19-24, 30, 34	11	All R	No	–	–	Quiescent
A19	HI-1	Cavitated	Placebo	23-25	6	All S	No	26	SZ (18)	Quiescent
A287	PH	Cavitated	Placebo	24, 27, 28	6	All S	Yes	29	PH (12)	Quiescent
A141	PH	Cavitated	Placebo	36, 39, 42	6	All S	Yes	43	PH (12)	Quiescent
A11	HI-1	Cavitated	Placebo	42, 45, 57, 59½, 60	6	S, R, S, S, S	No	–	–	Active
A229	HI-2	Cavitated	Isoniazid	14, 15, 19, 24	6	All R	Yes	26	SZ (13)	Quiescent
A61	HI-1	Non-cavitated	Placebo	14, 15	2	Both S	No	–	–	Quiescent
A156	PH	Non-cavitated	Placebo	18, 19	3	Both S	Yes	19	SZ (18)	Quiescent
A18	PH	Non-cavitated	Placebo	18, 20, 22, 24	8	All S	Yes	25	PH (11); SZ (6); CE (12)	Active
A275	HI-2	Non-cavitated	Placebo	19, 20, 23, 45	4	All S	No	–	–	Quiescent
A38	PH	Non-cavitated	Placebo	20-22	7	S, C, S	Yes	23	PH (14)	Quiescent
A20	H	Non-cavitated	Placebo	20-24, 27-31	15	All S	No	31	SP (12)	Died of tuberculous meningitis
A334	H	Non-cavitated	Placebo	36, 39, 42, 45-47	9	S, N, S, S, S, S	No	48	PH (12)	Active
A157	H	Non-cavitated	Placebo	17, 39, 42, 44, 45, 47	8	All S	No	47	PH (12)	Quiescent
A268	PH	Non-cavitated	Placebo	45, 46	3	R, S	Yes	46	SZ (12)	Quiescent
A31	PH	Non-cavitated	Placebo	54, 60	3	Both S	No	–	–	Active
A285	PH	Non-cavitated	Isoniazid	54, 59½	2	Both R	No	–	–	Active

[a] Up to start of re-treatment.
[b] S = sensitive; R = resistant; C = contaminated; N = not tested.
[c] H = isoniazid; P = PAS; S = streptomycin; Z = pyrazinamide; C = cycloserine; E = ethionamide.

investigated. The degree of smear positivity, the extent of cavitation and the radiographic extent of disease on admission to treatment were not associated with the likelihood of relapse, nor was there any association between the occurrence of relapse and the month of sputum conversion in the first year, the extent of cavitation at 1 year or the radiographic extent of disease at 1 year.

PATIENTS WITH ISOLATED POSITIVE CULTURES

Isolated positive cultures (defined on page 3) were produced by 29 patients, namely, 11 (16 %) of the PH, 5 (12%) of the HI-1, 6 (17%) of the HI-2 and 7 (21%) of the H patients; the proportion was 15% for the patients with cavitation at 1 year as compared with 17% for those without cavitation, and 14% for the patients in the placebo group as compared with 18 % for the patients in the isoniazid group. None of the differences was statistically significant.

In all, 31 isolated positive cultures were produced by the 29 patients–8 in the second year, 8 in the third year, 11 in the fourth year and 4 in the fifth year. Of these, 18 were from sputum specimens, 2 of which had a positive smear result. Considering all 31 cultures, the growth was a single colony in 12 and 2 colonies in 3; it was more than 100 colonies in only 4 cultures. The organisms were sensitive to isoniazid in 18 of 27 cultures tested (including 2 of 4 specimens produced while the patient was receiving isoniazid). Three of the 29 patients had produced isoniazid-resistant cultures in the *first year;* in 2, the isolated positive culture was sensitive to isoniazid and in the third, the test result was not available.

Finally, the occurrence of an isolated positive culture did not carry an unfavourable prognosis. Thus, only 1 (3 %) of the 29 patients with an isolated positive culture had a bacteriological relapse subsequently.

OTHER ASSESSMENTS OF PROGRESS

The findings of the radiographic assessments and erythrocyte sedimentation rate (ESR) determinations are presented below for the 157 patients who had bacteriologically quiescent disease *throughout the period of follow-up* (of the remaining 23 patients, 17 had a bacteriological relapse, 5 died of non-tuberculous causes and 1 patient refused to attend for assessment from the forty-fifth month onwards).

Changes in radiographic appearances

An independent assessor (Dr Raj Narain) assessed the over-all changes in radiographic appearances between 12 and 24, 24 and 36, and 36 and 60 months, by viewing standard postero-anterior radiographs. Improvement was reported in 29 %, 25 % and 18 % of the patients, respectively, including 27%, 25% and 18 % in whom it was graded as slight. The corresponding proportions for radiographic deterioration were 19%, 9 % and 20%, including 17 %, 7% and 17% in whom it was graded as slight.

Cavitation changes between 12 and 60 months were assessed by the independent assessor using standard radiographs and tomograms. There were 46 patients with cavitation at 1 year; it disappeared by 5 years in 52%, decreased in 24%, remained unchanged in 20% and increased in 4%. Of 111 patients with no cavitation at 1 year, 4 (4%) developed cavitation by 5 years.

Erythrocyte sedimentation rate

The ESR reading at 1 hour was measured on admission to treatment and, in most patients, at 1, 2, 3 and 4 years. The proportion of patients who had an elevated ESR (more than 10 mm) was 65% at 1 year, 46 % at 2, 61% at 3 and 54 % at 4 years. For an ESR of 21 mm or more, the corresponding proportions were 39%, 27 %, 36% and 32%, respectively, and for 51 mm or more, 12%, 8 %, 11% and 10 %, respectively.

In summary, there was general improvement over the 4-year period in the radiographic condition of the patients with persisting bacteriologically quiescent disease. However, minor radiographic changes interpreted as slight deterioration and elevated ESRs occurred in a fair proportion of these patients.

PATIENTS NOT INCLUDED IN THE RELAPSE STUDY

Of the 11 patients not included in the random allocation to treatment (see page 4), 6 (2 PH, 1 HI-1, 3H; 4 cavitated, 2 non-cavitated) continued to receive the treatment that they had had during the first year while the remaining 5 (2 PH, 1 HI-1, 1 HI-2, 1 H; 1 cavitated, 4 non-cavitated) received the placebo in the second year. Two of these patients had a bacteriological relapse. One patient (H, cavitated, isoniazid) had a relapse with isoniazid-resistant organisms in the fourteenth month; subsequently, positive cultures were occasionally ob-

tained until the twenty-ninth month (the patient received isoniazid in the third year also), and thereafter, the cultures were persistently negative up to the end of the period of follow-up. The other (PH, non-cavitated, placebo) had a bacteriological relapse with isoniazid-sensitive cultures (in the seventeenth month), was re-treated with isoniazid plus PAS, and had bacteriologically quiescent disease at 5 years.

One patient (PH, cavitated, placebo) developed tuberculous lymphadenitis, which was confirmed bacteriologically in the thirty-ninth month. She was re-treated with isoniazid plus PAS; all her sputum and laryngeal swab cultures during the 4-year period were negative.

IV. PATIENTS WITH DISEASE OF BACTERIOLOGICALLY DOUBTFUL STATUS AT 1 YEAR

Altogether, 9 patients (4 PH, 4 HI-1, 1 HI-2) were classified as having disease of bacteriologically doubtful status at one year; 3 had cavitation and 6 had no residual cavitation at 1 year; 6 received the placebo and 3 received isoniazid in the second year. Only 1 patient (HI-1, non-cavitated, isoniazid) had a bacteriological relapse. This relapse occurred at 17 months with isoniazid-resistant organisms; subsequently, the cultures were positive at 18, 20 and 22 months but were negative thereafter (the patient received isoniazid in the third year also), and the patient had bacteriologically quiescent disease at 5 years.

V. PATIENTS WITH BACTERIOLOGICALLY ACTIVE DISEASE AT 1 YEAR

Table 5 presents information on 96 patients (7 PH, 17 HI-1, 27 HI-2, 45 H) who had bacteriologically active disease at 1 year, including 35 (1 PH, 5 HI-1, 14 HI-2, 15 H) who had had their chemotherapy changed during the first year on account of deterioration. Of the latter 35 patients, 15 received 1 reserve regimen (streptomycin plus pyrazinamide or streptomycin plus PAS), 7 received 2 reserve regimens (the second usually being cycloserine plus ethionamide or cycloserine plus thioacetazone), and 13 received more than 2 reserve regimens. At 5 years, 15 (43%) patients had bacteriologically quiescent disease, 5 had bacteriologically active disease and 15 had died, 13 of tuberculosis and 2 of non-tuberculous causes.

Of the remaining 61 patients with bacteriologically active disease at 1 year, 58 continued on their initially allocated chemotherapy, 2 received isoniazid and 1 received the placebo. Of these, 33 (54%) had a change of chemotherapy for deterioration in the second year and 17 (28 %) had a change of chemotherapy (at 2 years in 13 of them) due to persistent sputum positivity; their subsequent progress is described below. The remaining 11 (18 %) patients had a late sputum conversion (10 of them by the beginning of the second year), *without* receiving any reserve regimen.

Of the 33 patients who had a deterioration in the second year, 25 received 1 reserve regimen, 5 received 2 and 3 received 3. At 5 years, 27 (82%) patients had bacteriologically quiescent disease, 3 had bacteriologically active disease and 3 had died, 2 of tuberculosis and 1 of a non-tuberculous cause.

Of the 17 patients who had a change of chemotherapy due to persistent sputum positivity, 13 received 1 reserve regimen and 3 received 2; the remaining patient, who discharged himself, received streptomycin plus isoniazid elsewhere. At 5 years, 12 (71%) patients had bacteriologically quiescent disease, 2 had bacteriologically active disease and 3 had died, 2 of tuberculosis and 1 of a non-tuberculous cause.

Patients who had a deterioration in the first year had a worse response subsequently than those who had a deterioration in the second year, for 13 (37 %) of 35 among the former died of tuberculosis as compared with 2 (6%) of 33 among the latter, a significant difference ($P<0.01$). However, the bacteriological and radiographic [1] condition *at the time of the deterioration* was worse for the patients

[1] The radiographs for the two groups were assessed concurrently by an independent assessor (Dr Raj Narain), in a random order.

TABLE 5
DISEASE STATUS AT 5 YEARS FOR PATIENTS WITH BACTERIOLOGICALLY ACTIVE DISEASE AT 1 YEAR

		Total patients	Disease status at 5 years				
			Quiescent		Active	Death	
			No.	%		Tuberculous	Non-tuberculous
Change of chemotherapy	Deterioration in the first year	35	15	*43*	5	13	2
	Deterioration in the second year	33	27 [a]		3	2	1
	Persistent sputum positivity	17	12[b]	*(71)*[c]	2	2 [d]	1
No change of chemotherapy	Late sputum conversion	11	11	*(100)*	0	0	0
Total		96	65	*68*	10	17	4

[a] Including 1 patient who had a lobectomy.
[b] Including 1 patient who was treated in another institution and who also had a thoracoplasty.
[c] Parentheses indicate that the percentage is based on fewer than 25 observations.
[d] Including 1 patient whose chemotherapy was changed on account of cor pulmonale.

who had the deterioration in the first year than for those who had the deterioration in the second year. Thus, (1) 80 % of the former had a 2+ or 3 + smear result as compared with 58 % of the latter (P=0.08); (2) 66% and 27%, respectively, had moderate or extensive cavitation (P <0.01); (3) 66% and 18 %, respectively, had 5 or 6 lung zones involved (P< 0.001); (4) 63 % and 18 %, respectively, had moderate, extensive or gross disease (P<0.001); and (5) 31 % and 6%, respectively, had moderate or considerable radiographic deterioration [1] in the month just preceding the change of chemotherapy (P = 0.02). Furthermore, analyses not tabulated here showed that the patients in the categories (1), (2), (3), (4) and (5) had a relatively unfavourable prognosis. Finally, 8 of the patients who had the deterioration in the first year received a regimen of cycloserine plus thioacetazone which was rather ineffective (Angel et al., 1963), as compared with none of the patients who had the deterioration in the second year. It may therefore be concluded that the substantially worse response among the patients who had the deterioration in the first year was due to several factors.

VI. PATIENTS WHOSE TREATMENT WAS CHANGED FOR DRUG TOXICITY DURING THE FIRST YEAR

Seven patients (1 PH, 5 HI-1, 1 HI-2) had their treatment changed in the first year due to drug toxicity. The PH patient had hypersensitivity to PAS and was prescribed streptomycin plus isoniazid; the remaining 6 had peripheral neuropathy due to isoniazid and were prescribed a reserve regimen (followed by a second reserve regimen in 2). An eighth patient (PH) was successfully desensitized to PAS over a 3-month period. All 8 had bacteriologically quiescent disease at 5 years.

[1] The radiographs for the two groups were assessed concurrently by an independent assessor (Dr Raj Narain), in a random order.

VII. PATIENTS EXCLUDED FROM THE MAIN ANALYSIS

Of the 26 patients excluded from the main analysis, 22 had isoniazid-resistant organisms on admission (acquired resistance in 2 and primary resistance in 20). Considering first the 2 patients with acquired isoniazid resistance, 1 died of a non-tuberculous cause while under treatment with streptomycin plus pyrazinamide, and the other had bacteriologically active disease at 5 years despite receiving 2 reserve regimens, namely, streptomycin plus pyrazinamide and cycloserine plus ethionamide.

Of the 20 patients with primary isoniazid resistance, 2 died of tuberculosis in the first year. Three patients had bacteriologically quiescent disease at 1 year and maintained it up to 5 years, 2 having received isoniazid alone in the second and third years and 1 having received no chemotherapy after the first year. Of the remaining 15 patients, all of whom had bacteriologically active disease at 1 year, (1) 10 had bacteriologically quiescent disease at 5 years; of these, 1 had received no reserve regimen, 7 had received 1 reserve regimen, 1 had received 2 regimens, and 1 had surgical collapse therapy in addition to 4 regimens; (2) 3 patients had bacteriologically active disease at 5 years, despite 1 reserve regimen in 1 and 3 regimens in 2; and (3) 2 patients died of tuberculosis, 1 while receiving his first reserve regimen, and the other, 13 months after discontinuing his second reserve regimen.

In summary, 13 of 20 patients with primary isoniazid resistance had bacteriologically quiescent disease at 5 years, 3 had bacteriologically active disease and 4 had died from tuberculosis.

Of 4 patients excluded from the main analysis for miscellaneous reasons, 1 had died of a non-tuberculous condition in the first year, and the remaining 3 had bacteriologically quiescent disease at 5 years without receiving any reserve regimen.

VIII. DISEASE STATUS AT 5 YEARS OF ALL PATIENTS

The disease status at 5 years of the 96 PH, 75 HI-1, 75 HI-2 and 95 H patients is set out in Table 6. During the 5-year period, 16 patients died of non-tuberculous causes. Of these, 6 (2 PH, 1 HI-1, 1 HI-2, 2 H) died in the first year and have been reported previously (Tuberculosis Chemotherapy Centre, Madras, 1960). Of the remaining 10 patients, 7 (2 PH, 2 HI-1, 3 H) had had all cultures negative for at least 12 months before death; the other 3 (1 HI-1, 2 H) had become culture-negative 1, 1 and 2 months, respectively, before death.

One patient (HI-2) discharged himself from follow-up in the forty-fifth month, having had all cultures negative from the second month onwards; he was known to be alive at 5 years.

Of the remaining 92 PH, 71 HI-1, 73 HI-2 and 88 H patients (including 21 of the 22 patients with initial isoniazid resistance), 91%, 90%, 86% and 76 %, respectively, had bacteriologically quiescent disease at 5 years, 4%, 6%, 4% and 9 % had bacteriologically active disease, and 4%, 4%, 10% and 15 %, respectively, had died of tuberculosis. Considering all the patients in the 4 series combined, 86% of the patients had bacteriologically quiescent disease at 5 years, 6% had bacteriologically active disease and 8 % had died of tuberculosis.

It will be recalled that the general policy was to treat patients at home. In the event, 61 patients (11 PH, 9 HI-1, 14 HI-2, 27 H), namely 18 %, were hospitalized during the 5-year period for tuberculous conditions, the period of hospitalization being less than 1 month in 13, 1-3 months in 11, 3-6 months in 13, 6-12 months in 14 and 1 year or more in 10.

TABLE 6
DISEASE STATUS AT 5 YEARS FOR ALL PATIENTS ADMITTED TO STUDY

	Disease status [a] at 5 years																			
	PH patients					HI-1 patients					HI-2 patients					H patients				
	Total	Quiescent		Active	Tuberc. death	Total	Quiescent		Active	Tuberc. death	Total	Quiescent		Active	Tuberc. death	Total	Quiescent		Active	Tuberc death
		No.	%				No.	%				No.	%				No.	%		
Patients included in the main analysis:																				
(1) Bacteriologically quiescent disease at 1 year	72	69	*96*	3	0	41	40	*98*	1	0	36	36	*100*	0	0	37	35	*95*	1	1
(2) Disease of bacteriologically doubtful status at 1 year	4	4	*(100)* [b]	0	0	4	4	*(100)*	0	0	1	1	*(100)*	0	0	0	—	—	—	—
(3) Bacteriologically active disease at 1 year	7	6	*(86)*	0	1	17	11	*(65)*	3	3	27	20	*74*	1	6	41	28	*68*	6	7
(4) Treatment changed for drug toxicity in the first year	2	2	*(100)*	0	0	5	5	*(100)*	0	0	1	1	*(100)*	0	0	0	—	—	—	—
(5) Tuberculous death in the first year	1	—	—	—	1	0	—	—	—	—	1	—	—	—	1	3	—	—	—	3
Patients excluded from the main analysis:																				
(1) Isoniazid-resistant organisms on admission	6	3	*(50)*	1	2	2	2	*(100)*	0	0	7	5	*(71)*	2	0	6	3	*(50)*	1	2
(2) Miscellaneous reasons	0	—	—	—	—	2	2	*(100)*	0	0	0	—	—	—	—	1	1	*(100)*	0	0
Total patients	92	84	*91*	4	4	71	64	*90*	4	3	73	63	*86*	3	7	88	67	*76*	8	13
Non-tuberculous death during the 5-year period	4	—		—	—	4	—		—	—	1	—		—	—	7	—		—	—
All patients admitted to study	96	—		—	—	75	—		—	—	75 [c]	—		—	—	95	—		—	—

[a] For details, see page 11.
[b] Parentheses indicate that the percentage is based on fewer than 25 observations.
[c] Including 1 patient lost to observation in the forty-fifth month.

IX. DISCUSSION

A previous communication from this Centre reported on the progress during a 5-year period of 193 patients with newly diagnosed, bacteriologically confirmed pulmonary tuberculosis, who were admitted to a concurrent comparison of home and sanatorium treatment for 1 year with isoniazid plus PAS (Dawson et al., 1966). The present paper reports on the progress, also over a 5-year period, of a similar group of 341 patients, all of whom were treated at home with isoniazid plus PAS or 1 of 3 regimens of isoniazid alone for a year. Since the management of patients and the intensity of investigations in the 2 studies were practically identical, it is convenient to review the findings of both studies together.

The bacteriological relapse rate during the 4-year period of follow-up (among those who had bacteriologically quiescent disease at 1 year) was 8.7 % of 126 in the earlier study and 9.4% of 180 in the presen-study (it will be recalled that half the patients, selected at random, received maintenance chemotherapy with isoniazid in the second year). There was no evidence that the relapse rate was influenced by the chemotherapeutic regimen received in the first year; thus, for the isoniazid plus PAS regimen, it was 8.7 % of 126 in the earlier study and 13 % of 69 in the present study (that is, 10% in both studies combined), as compared with 7% of 41, 6% of 36 and 9% of 34 for the 3 regimens of isoniazid alone.

Isoniazid alone, given as maintenance therapy in the second year, was highly effective in preventing bacteriological relapse in patients who, at 1 year, had bacteriologically quiescent disease and no residual cavitation. Thus, in the earlier study, none of 42 such patients had a bacteriological relapse in the 4-year period of follow-up as compared with 7 (17 %) of 42 who received a placebo, the corresponding proportions in the present study being 1 (2 %) of 61 and 10 (15 %) of 65, respectively. Both these differences are significant (P=0.01). However, in patients with residual cavitation at 1 year, the benefit from isoniazid in the second year was less marked. Thus, in the earlier study, 3 of 23 patients who received isoniazid had a bacteriological relapse in the 4-year period of follow-up as compared with 1 of 19 who received a placebo, the corresponding proportions in the present study being 1 of 32 and 5 of 22, respectively. Combining the results of the 2 studies, 4 (7%) of 55 who received isoniazid had a bacteriological relapse as compared with 6 (15 %) of 41 who received a placebo (P=0.4).

In both studies, a subsidiary investigation, *based on random allocation,* was undertaken to determine the value of continuing isoniazid for the third year in patients who had received isoniazid alone in the second year. In the earlier study, there were no bacteriological relapses in the third, fourth or fifth years in 30 patients who received isoniazid in the third year, but neither were there any relapses in 30 patients who received only a placebo in the third year. The corresponding proportions in the present study were 1 of 47 for the isoniazid group and none of 44 for the placebo group. Thus, as there were no relapses in either study in the patients who had received a placebo in the third year, there was really no scope for the isoniazid to prevent relapse. (As far as we are aware, these 2 studies are the only controlled investigations that compare the relative merits of 1 year and 2 years of maintenance treatment with isoniazid alone in the prevention of relapse in patients with bacteriologically quiescent disease at 1 year.) This finding emphasizes the need to have suitable control groups for accurate interpretation of the findings of chemotherapy studies and, in particular, the need for caution in assessing recommendations made by some workers for very prolonged or indefinitely prolonged chemotherapy to prevent relapse (Dooneief et al., 1955; Hyde, 1960; Pfuetze et al., 1960; Worobec et al., 1960).

For developing countries with limited resources, the relapse rate in patients who received only 1 year of antituberculosis chemotherapy is of special interest. Of 148 such patients in the 2 studies combined, 23 (15.5%) had a bacteriological relapse during the 4-year period of follow-up. The relapse rate was appreciable in the second year, namely, 9.5%, and uniformly small in subsequent years, namely, 2.0 % in the third, 2.0 % in the fourth and 2.0 % in the fifth year. Further, it was unaffected by the cavitation status of the patient at 1 year, 6 (15%) of 41 patients with the " open-negative " syndrome having a bacteriological relapse during the 4-year period, as compared with 17 (16%) of 107 patients who had no residual cavitation at 1 year, including 10 % and 9 %, respectively, in the second year. These findings suggest that, in countries with limited resources, long-term follow-up beyond 2 years should be given a very low level of priority, even if the patients have

residual cavitation at 1 year. Further, of the relapses in the second year, the great majority (11 of 14 in the present report) can be detected by culture examinations at 24 months, or earlier, if the patients present with symptoms.

Isolated positive cultures, often with a growth of only a few colonies and frequently isoniazid-sensitive, occurred in the 4-year period of follow-up in 14% of the patients in the earlier study and 16% of the patients in the present study. Their occurrence is not very surprising (especially as the intensity of bacteriological examination was high-namely, over 40 cultures during the 4-year period) since, even after prolonged and appropriate chemotherapy, viable tubercle bacilli may be present in the lungs (McDermott, 1959) and, indeed, in the sputum (Great Britain, Medical Research Council, 1962). Further, it was of little clinical importance, as only 6 % of such patients in the earlier study and 3 % in the present study had a bacteriological relapse subsequently. These findings suggest that chemotherapy should not be restarted on the strength of a single positive culture, but should at least await 1 or more confirmatory positive cultures within the next few months.

An elevated ESR (that is, more than 10 mm) was not uncommon in patients with bacteriologically quiescent disease throughout the 4-year period of follow-up. Thus, the proportion of patients with such a finding at the yearly examinations ranged from 60 % to 75 % in the earlier study, and from 46% to 65% in the present study. These findings demonstrate that measurements of ESR can often be misleading in following the progress of patients with bacteriologically quiescent disease. Similar findings have also been reported from East Africa (Hutton et al., 1956) and from the United Kingdom (Great Britain, Medical Research Council, 1962).

In the treatment of patients with bacteriologically active or relapsed disease with isoniazid-resistant organisms, streptomycin plus pyrazinamide, streptomycin plus PAS and cycloserine plus ethionamide proved to be useful regimens (see Velu et al., 1960, 1961b, 1964; Angel et al., 1963; Ramakrishnan et al., 1967).

Finally, considering the disease status at 5 years of all the patients admitted to study (but excluding deaths due to non-tuberculous causes), 90% in the earlier study and 86% in the present study had bacteriologically quiescent disease. These findings are very encouraging, especially as nearly half the patients (in the 2 studies combined) received isoniazid alone as the primary regimen. Furthermore, the follow-up in both studies was exceptionally good, none of 193 patients in the earlier study and only 1 of 341 patients in the present study being permanently lost to observation. The remarkable degree of success achieved in following the patients for 5 years was due to (1) the selection initially of *bona fide* residents regarded as co-operative, (2) efficient appointment systems, and (3) well-organized domiciliary service.

In conclusion, the earlier study demonstrated that patients with extensive sputum-positive tuberculosis, living in very adverse environmental, dietary and economic conditions, can be treated successfully in their homes (Dawson et al., 1966; Ramakrishnan et al., 1966). The present study has provided confirmation of the value of well-organized domiciliary chemotherapy.

X. SUMMARY

1. A total of 341 patients was admitted to a controlled comparison of a standard oral regimen of isoniazid plus PAS (PH) for 1 year with 3 oral regimens of isoniazid alone, namely, 400 mg a day in 1 dose (HI-1), 400 mg a day in 2, divided, doses (HI-2), and 200 mg a day in 2, divided, doses (H).

2. Of the 341 patients, 315 had isoniazid-sensitive cultures on admission and were included in the main analysis in the first year, and 26 were excluded because they did not conform to this or other important criteria.

3. Of the 315 patients, 192 had bacteriologically quiescent disease at 1 year, 9 had disease of bacteriologically doubtful status, 96 had bacteriologically active disease, 10 had died (5 of tuberculosis and 5 of non-tuberculous causes) and 8 had had their treatment changed on account of drug toxicity.

4. Of the 192 patients with bacteriologically quiescent disease at 1 year, 180 (69 PH, 41 HI-1, 36 HI-2, 34 H) were randomly allocated to treatment for the second year with isoniazid alone or a placebo; of these 180 patients, 126 had no residual cavitation at 1 year.

5. During the 4-year period of follow-up, 17 (9.4%) of the 180 patients had a bacteriological relapse, 10 of them in the first year of follow-up. The proportion with a relapse was 13% in the PH series, as compared with 7 %, 6 % and 9% in the HI-1, HI-2 and H series, respectively.

6. Of the 126 patients with no residual cavitation at 1 year, 10 (15 %) of 65 in the placebo group had a bacteriological relapse compared with 1 (2 %) of 61 in the isoniazid group (P=0.01). Of the 54 patients with residual cavitation at 1 year, 5 (23 %) of 22 in the placebo group had a bacteriological relapse compared with 1 (3 %) of 32 in the isoniazid group (P = 0.07).

7. A total of 91 patients, who had received isoniazid in the second year, were allocated at random to treatment for the third year, 47 to isoniazid alone and 44 to placebo; 1 and 0, respectively, had a bacteriological relapse during the third, fourth or fifth years.

8. Of 29 (16%) patients who produced isolated positive cultures during the 4-year period of follow-up, only 1 had a bacteriological relapse subsequently.

9. Of the 9 patients with disease of bacteriologically doubtful status at 1 year, 1 patient had a bacteriological relapse, in the seventeenth month.

10. Of the 96 patients in the main analysis who had bacteriologically active disease at 1 year, 84 were re-treated with 1 or more reserve regimens. At 5 years, 65 (68%) of the 96 patients had bacteriologically quiescent disease, 10 (10%) had bacteriologically active disease, and 21 had died, 17 (18 %) from tuberculosis and 4 (4%) from non-tuberculous causes.

11. Of 20 patients excluded from the main analysis because they had *primary* isoniazid resistance organisms, 13 (65 %) had bacteriologically quiescent disease at 5 years, 3 had bacteriologically active disease and 4 had died from tuberculosis.

12. Of the total of 341 patients admitted to the study, 16 died from non-tuberculous causes during the 5-year period and 1 took his discharge prematurely. Of the remaining 324, 86 % had bacteriologically quiescent disease at 5 years, 6% had bacteriologically active disease and 8% had died of tuberculosis.

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RÉSUMÉ

ÉTUDE COMPARATIVE CONTRÔLÉE DU TRAITEMENT À DOMICILE DE LA TUBERCULOSE PULMONAIRE PAR L'ASSOCIATION ISONIAZIDE-PAS OU PAR L'ISONIAZIDE SEUL SELON TROIS SCHÉMAS DIFFÉRENTS: ANALYSE DE L'ÉVOLUTION CHEZ DES PATIENTS SUIVIS PENDANT CINQ ANS

Au cours d'une etude comparative de divers traitements de la tuberculose pulmonaire, on a administré sous contrôle, pendant un an, à un groupe de 341 malades soit le schéma standard (PH) comportant en deux doses quotidiennes 200 mg d'isoniazide et 10 g de PAS, soit de l'isoniazide seul à raison de 400 mg par jour en une dose unique (schema HI-l), de 400 mg par jour en deux doses (schema HI-2) ou de 200 mg par jour en deux doses (schema H). Sur ces 341 malades, 315 qui étaient porteurs avant le traitement de bacilles sensibles à l'isoniazide ont été inclus dans l'enquête principale de la 1re année; 26 sujets en ont été éliminés pour resistance à l'isoniazide ou pour d'autres raisons.

Sur ces 315 malades, 192 présentaient après un an une affection bactériologiquement non évolutive; chez 9 autres, les examens bactériologiques donnaient des résultats d'interpretation malaisée; 96 cas enfin étaient bactériologiquement actifs. Dix déces ont été enregistrés (5 dus à la tuberculose, 5 dus à d'autres causes). Chez 8 malades, on a modifié le traitement en raison de la toxicité des médicaments.

Cent quatre-vingts des 192 malades qui ne montraient aucun signe bactériologique d'évolution après un an, soit 69 PH, 41 HI-1, 36 HI-2 et 34 H, ont été traités sur une base aléatoire pendant Ia 2e année par l'isoniazide seul ou par placebo. Sur ces 180 malades, 126 ne présentaient après la 1re année de traitement aucune cavité résiduelle. Au cours des 4 années suivant la 1re année de traitement, 17 (9,4 %) des 180 patients ont présenté une rechute bactériologique (deux cultures positives, ou davantage, au cours d'une période de 6 mois), survenue chez 10 d'entre eux, dans l'année suivant le traitement. La proportion des rechutes a été de 13 % dans le groupe PH et de 7%, 6% et 9 % respectivement dans les groupes HI-1, HI-2 et H.

Parmi les 126 malades chez lesquels ne persistait après un an de traitement aucune cavité résiduelle, 10 (15 %) des 65 malades appartenant au groupe placebo ont souffert d'une rechute bactériologique, alors qu'une telle rechute n'a été observée que chez un seul (2%) des 61 malades traités par l'isoniazide (P=0,01). Sur les 54 patients qui, après un an, présentaient des cavités residuelles, 5 (23%) des 22 malades du groupe placebo ont eu une rechute bactériologique, qui ne s'est produite que chez 1 (3%) des 32 malades du groupe traité par l'isoniazide (P=0,07).

Un total de 91 malades traités par l'isoniazide pendant Ia 2e année ont reçu par randomisation au cours de la 3e année soit de l'isoniazide seul (47 sujets) soit un placebo (44 sujets). On a enregistré dans ces groupes respectivement 1 et 0 rechute bactériologique au cours de Ia 3e, de la 4e ou de la 5e année de surveillance de l'évolution.

Sur les 29 (16%) malades qui ont présenté une culture positive isolée (c'est-à-dire avec négativite des cultures 6 mois avant et 6 mois après cet examen positif), au cours des quatre années de surveillance après traitement, une seule rechute bactériologique a été enregistrée par la suite. Un seul des 9 cas « douteux » du point de vue bactériologique a eu une rechute bactériologique au 17e mois.

Quatre-vingt quatre des 96 malades inclus dans l'etude principale chez qui on décelait après un an une affection bactériologiquement Obvolutive ont bénéficié d'un nouveau traitement suivant un ou plusieurs schémas non encore utilisés. Après 5 ans, 65 (68%) de ces 96 malades présentaient une affection bactériologiquement non évolutive et 10 (10%) une tuberculose bactériologiquement active. 11 s'etait produit 21 décès dont 17 (18%) dus à la tuberculose et 4 (4 %) causes par d'autres maladies.

Parmi les 20 malades exclus de l'étude principale pour resistance primaire à l'isoniazide, 13 (65 %) présentaient après 5 ans une affection bactériologiquement non évolutive et 3 une affection bactériologiquement active. Il y a eu 4 décès par tuberculose.

Sur le total de 341 patients inclus dans l'étude, 16 sont morts d'affections autres que la tuberculose au cours de la période de 5 ans et 1 a cessé prématurément son traitement. Après 5 ans, sur les 324 malades restants, 86% présentaient une affection bactériologiquement non évolutive et 6 % une tuberculose en evolution. On a enregistre 8% de décès par tuberculose.

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